Synopsis

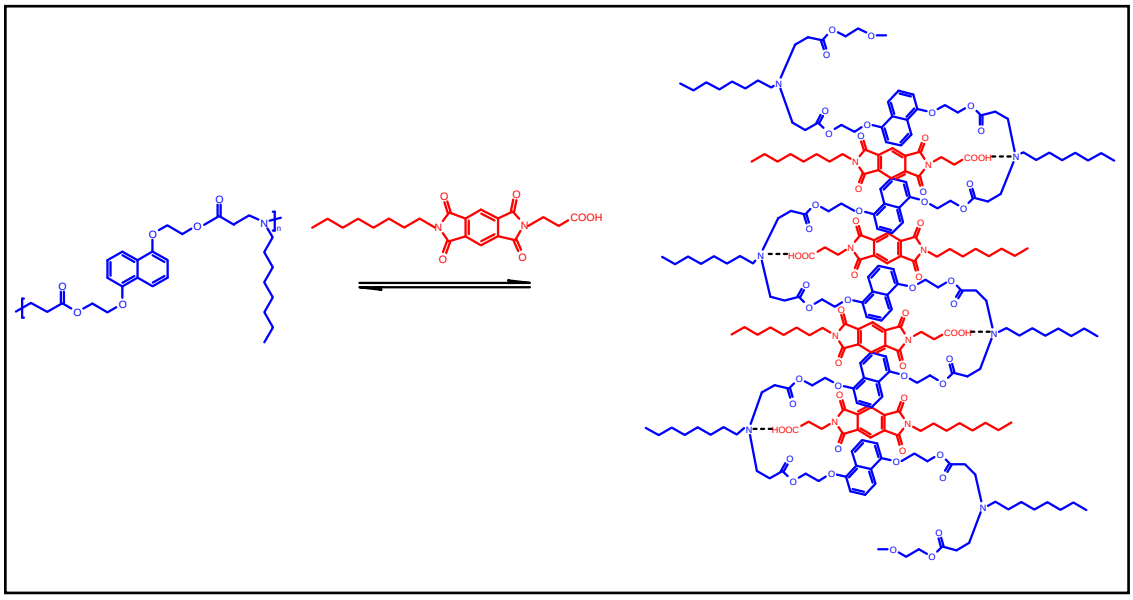
This thesis contains investigations in two different areas, described under six chapters. Chapter 1 contains a broad introduction to the area of foldamers, while Chapters 2, 3, 4, and 5 deal with various novel classes of synthetic polymers which can form folded structures in solution utilizing different non-covalent interactions. Chapter 6 deals with a distinctly different topic, where the objective was to study the effect of phenyl ring location on the micellization properties of a series of isomeric cationic surfactants.

Synthetic polymers typically adopt a random coil conformation in solution, which is primarily an entropy driven process. So the generation of well-defined secondary structures in synthetic polymers requires specific intra-chain inter-segment interactions that will give adequate enthalpic contribution to overcome the entropic penalty associated with the formation of well-ordered conformations. During the past decade, various research groups have made significant effort to understand the essential design elements that could enable secondary structure formation in synthetic macromolecules through intra-chain inter-segment interactions, such as hydrogen bonding, solvophobic and solvophilic interaction, acid-base interaction, bond angle constraint, steric interaction, charge-transfer interaction, metal-ion complexation etc.[1] Gellman[2] first used the term "*foldamer*" to describe "*any polymer with a strong tendency to adopt a specific compact conformation*" which was more precisely defined by Moore and coworkers[3] as "*any oligomer that folds into a conformationally ordered state in solution, the structures of which are stabilized by a collection of non-covalent interactions between nonadjacent monomer units*" and where the folded conformation is one of the various possible conformations.

Several classes of foldamers have been studied during the past decade; a majority of them are well-defined oligomers that possess relatively restricted conformational degrees of freedom. Relatively fewer studies have explored conformational control in flexible high molecular weight polymers that possess greater conformational freedom.[4] A few years ago, Ghosh et al. designed a polymeric system wherein charge-transfer interactions between alternatively placed electron-rich and electron-deficient aromatic units, aided by metal-ion complexation and solvophobic interactions, causes the polymer chain to adopt a specific folded conformation.[5] Such

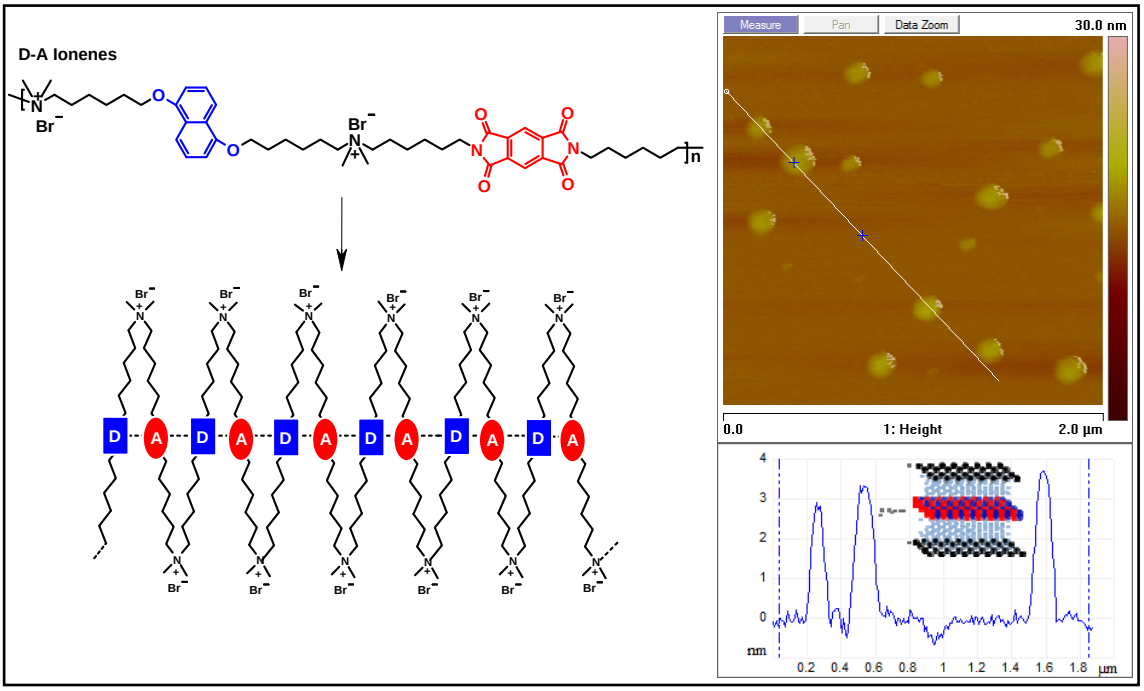
charge-transfer induced folding was first studied by Iverson and co-workers[6] in well-defined oligomers and was later elaborated by Zhao et al.[7] to generate alternate designs to fold oligomeric systems. In all these studies, the C-T interactions served not only to assist the folding process but it also served as a valuable spectroscopic signature to study the folding process.

The objectives of the present study are to develop simple synthetic strategies to generate different types of polymers that could be fold in solution using various noncovalent interactions. We have developed a simple synthetic strategy to design a new type of donor (1,5-dialkoxynaphthalene-DAN) containing polymer that carries a tertiary amine unit in the spacer segment, which could interact strongly with a suitably designed acceptor (pyromellitic diimide-PDI) bearing folding agent that carries a carboxylic acid group, as shown in Scheme 1.[8] This acid-base interaction, brings the acceptor unit in a suitable position so as to form a C-T complex with the adjacent donors, resulting in the folding of the polymer chain. The folded conformation was studied using UV-vis and NMR spectroscopy and the folding propensities were rationalized using DFT studies. The highest association constant between the folding agent and the polymer was estimated to be around 1200 M^{-1}.

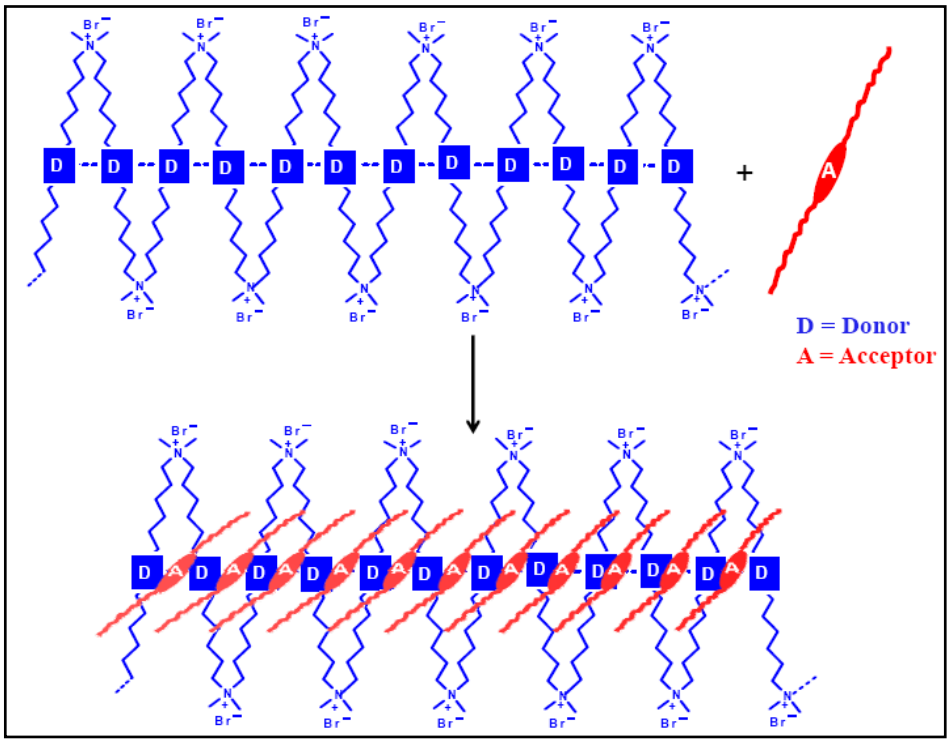


Scheme 1. *Schematic representation of folding aided by two-point interactions with a folding agent.*

This value of association constant was not adequate to realize some potentially interesting properties in solid state. In an attempt to develop alternate systems, that could exhibit stronger propensity to fold, we designed a new type of cationic ionene,[9] wherein electron-rich (DAN) and electron-deficient (PDI) aromatic units were included within the alkylene segments in an alternating fashion, as shown in Scheme 2.[10] The charge-transfer (C-T) interaction between the donor and acceptor units in neighbouring segments of the ionene not only reinforced the transition to the collapsed nano-bundle form but also provides a useful spectroscopic handle to monitor the conformational change. The UV-visible spectra of these novel D-A ionene solutions at a fixed concentration in four different solvents, namely water, methanol, acetonitrile and DMSO, show different extents of charge-transfer interaction. The colour of the solution in water was deep-red, whereas in acetonitrile, it was light-yellow. The conformational transition could also be induced by titrating an acetonitrile solution of the ionene with increasing amounts of water causing a dramatic increase in the intensity of the charge-transfer band, which reflects the extent of collapse to the zig-zag state that brings the donor and acceptor units together. AFM studies confirmed the presence of flat pancake-like aggregates having nearly constant height of about 3-5 nm, which was in accordance with the estimated thickness of the postulated zig-zag structure.



Scheme 2. *Schematic depiction of folding of D-A ionene (left), AFM micrograph showing pancake-like aggregates of D-A ionenes (right-top), a line scan depicting the heights and diameters of the aggregates along with a schematic depiction of the aggregate (right-bottom).*

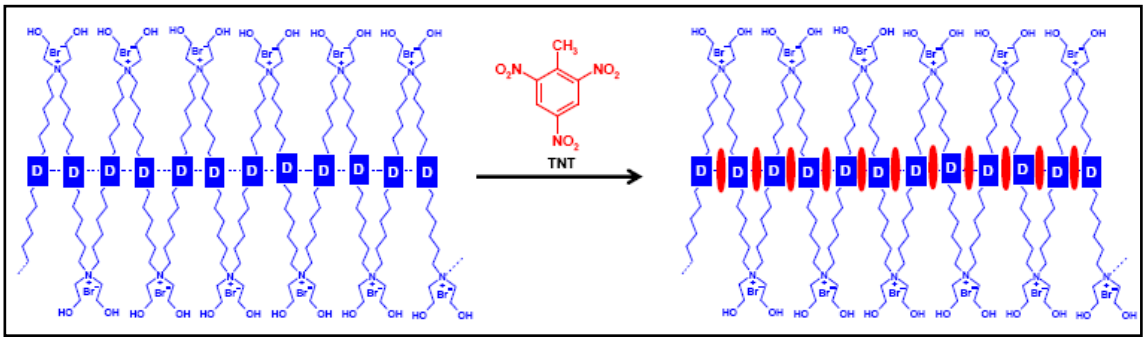


Scheme 3. *Schematic representation of folding aided by interactions with a folding agent.*

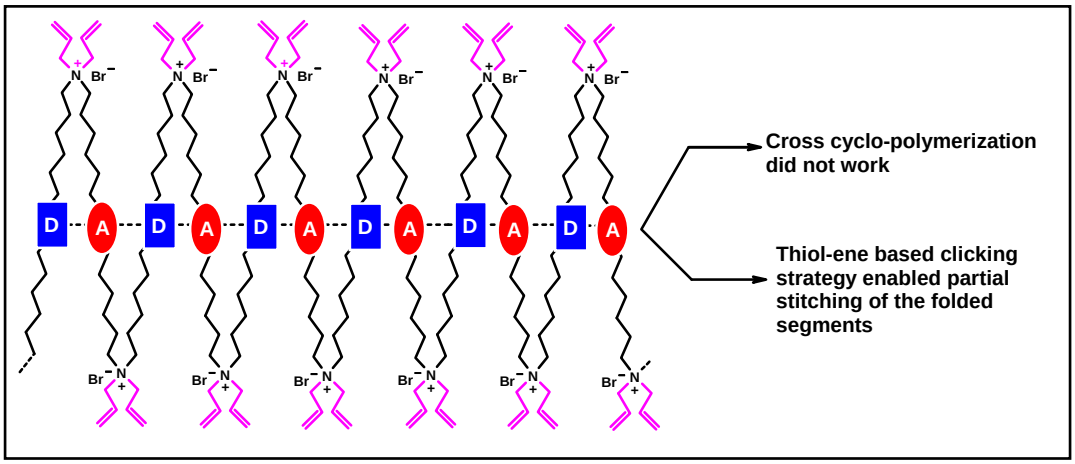
In order to explore this concept further, we designed a two component system wherein the solvophobically-driven collapse of a DAN-containing ionene chain in a polar solvent is reinforced by intercalation with a suitably designed electron-deficient acceptor-containing external folding agent. DAN containing ionene polymer chains in polar solvent form an accordion-type zig-zag structure that brings adjacent donor units in close proximity; this provided an ideal hydrophobic pocket for intercalation of suitably designed electron-deficient acceptor molecules, the additional driving motivation for the intercalation being the formation of a C-T complex as shown in Scheme 3.[11] Several acceptor-bearing molecules were prepared by the derivatization of pyromellitic dianhydride and naphthalene tetracarboxylic dianhydride with two different oligoethylene glycol monomethyl ether monoamines. UV-vis spectroscopic studies were carried out by using a 1:1 mixture of the DAN-ionenes and different acceptor molecules in water/DMSO solvent mixtures. The intensity of the charge-transfer (C-T) band was seen to increase with the water content in the solvent mixture, thereby suggesting that the intercalation is indeed aided by solvophobic effects. The naphthalene diimide (NDI) bearing acceptor molecules consistently formed significantly stronger C-T complexes when compared to the pyromellitic diimide (PDI) bearing acceptor molecules, which is

a reflection of the stronger π-stacking tendency of the former. The highest association constant between the folding agent and the polymer was estimated to be around 4519 M^{-1}, which was a substantial improvement over the earlier reported values.[9]

With a slight modification in the pendant group, we designed a water-soluble DAN-containing ionene, which can intercalate hydrophobic electron-deficient molecules, like TNT (2,4,6-trinitrotoluene), within the hydrophobic interstices between DAN units (as shown in Scheme 4), causing a depletion in fluorescence from the DAN units; TNT at concentration as low as 30 nM could be detected in this manner.



Scheme 4. *Schematic representation of folding of water soluble ionene and interactions with an electron-deficient hydrophobic moiety TNT.*

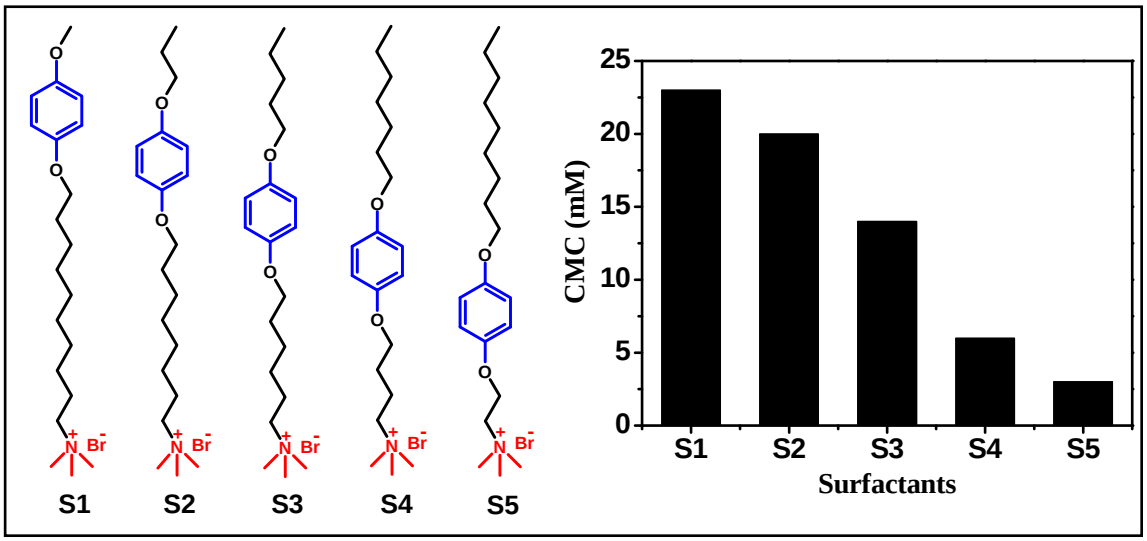


Scheme 5. *Schematic representation of folded D-A allyl ionene.*

In light of the growing interest in single-chain polymeric nanoparticles, the fully collapsed D-A ionenes in water could be viewed as polymeric nanoparticles that are stitched together by reversible weak noncovalent interactions. In an attempt to transform

the folded structure into a polymeric nanoparticle using covalent bonding, we designed D-A ionene that carries potentially polymerizable allyl units on the cationic head group instead of the dimethyl amine head group that was used in previous examples (as shown in Scheme 5). Preliminary studies showed that polymerization does not proceed readily; however, thiol-ene based clicking strategy enabled partial stitching of the folded segments, by the use of a suitably designed dithiol.

In the last section of this thesis, we examined the effect of phenyl ring location on the micellization properties of a series of isomeric cationic surfactants, wherein the phenyl ring location was varied from head to tail region (as shown in Scheme 6).[12] Thus, cationic surfactants (**S1-S5**) bearing a long alkyl chain that carries a 1,4-phenylene unit and a trimethyl ammonium headgroup was synthesized and their solution properties were examined. Micellization behavior was studied using conductivity, ITC (Isothermal Titration Calorimetry), SANS (Small-Angle Neutron Scattering) and NMR. These present studies demonstrated that the presence of a large rigid ring near the hydrocarbon tail-end of the surfactant leads to a dramatic change in the micelle structure; the driving motivation to form micelles in such systems is greatly reduced and the micelles that are formed are relatively smaller and contain significantly fewer surfactants. NMR studies of micellar solutions of these surfactants indicate that the variation in the phenyl ring location may also help to probe the microenvironment at various depths within the micellar aggregates.



Scheme 6. *Structures of the various surfactant molecules carrying the 1,4-dioxyphenylene unit at different locations within hydrophobic segment (left), variation of CMC values (right).*

References

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